NTP
National Toxicology Program

Research Concept: Bisphenol AF

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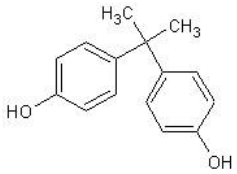
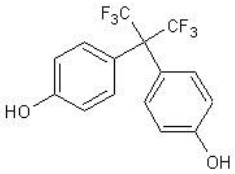
Nomination

- Numerous toxicological effects have been associated with bisphenol A (BPA) in mammals, depending upon the level of exposure
  - Effects on reproduction and development and other endocrine-related biological effects
- NTP CERHR Brief on BPA
  - *Some concern* for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures
- Bisphenol AF (BPAF) was nominated following an NTP review of BPA-related chemicals, based on:
  - Moderate production and use as a monomer for polyimides, polyamides, polyesters, polycarbonates, and other specialty polymers
  - Estrogenic activity
  - Lack of adequate toxicity data



Bisphenol A



Bisphenol AF

Production, Use and Human Exposure

- US annual production - 10,000 - 500,000 pounds
- NIOSH National Occupational Exposure Survey (1981-1983)
  - Estimated 4388 employees (1460 females) potentially exposed
- Use information is very limited
  - Monomer in polycarbonates and epoxy resins, and possibly in food-contact polymers
- Predicted to be persistent in the environment
  - Presence of six fluorine atoms in the molecule
- Found in extracts of human female adipose tissue
- Production and use patterns suggest that human exposure to BPAF is much lower than to BPA

Endocrine Activities of Bisphenol AF

- It appears that BPAF has greater estrogenic activity than BPA, based on:
  - In vitro reporter gene assay
  - Uterotrophic assay
- BPAF may have other endocrine activities, including:
  - Anti-androgenic
    - In vitro reporter gene assay
    - Not confirmed by Hershberger assay
  - Anti-estrogenic effects - inhibition of estrogenic effects upon co-exposure with potent estrogens
    - In vitro vitellogenin production
    - Uterotrophic assay
- BPAF binds ERRγ
  - Binding affinity much less than with BPA
- The uterotrophic and Hershberger assays are the only in vivo studies reported in the literature for BPAF
  - No other information available to characterize toxicity

Key Issues

- Does BPAF have toxicity similar to that of other synthetic estrogens?
- Do structure-activity relationships exist among the compounds belonging to the class of BPA-related compounds?
  - The NTP is currently considering class approaches for evaluating the toxicity of BPA-related compounds

Proposed Approach

- Overall goal: to better understand the toxicology of BPAF
- Hypothesis: Observed toxicities will be characteristic of a synthetic estrogen
- Key components:
  - Exposures
    - Route - oral
    - Inclusion of gestational and lactational periods
    - Wide spacing of doses
  - Disposition studies
  - Endpoints to characterize endocrine-related toxicities

Proposed Approach

- Tiered approach to research program:
  - Tier one study
    - Initial toxicological characterization
  - Tier two studies
    - Follow-up studies
    - Will be considered following review of toxicity data and future data on production, use, and exposure

Specific Aims

Tier one

Specific Aim 1: Conduct a transgenerational assay

- Rats exposed to a wide range of doses from gestation → sexual maturity (GD 6 → ~PND 100)
- Inclusion of both standard toxicity endpoints and sensitive endpoints to detect endocrine-related phenotypic effects
  - Onset of puberty in males and females
  - Uterine weight
  - Development of mammary tissue
- Analysis of disposition
- This study will characterize the toxicity of BPAF with emphasis on endocrine-related effects

Tier two

Specific Aim 2: Conduct absorption, distribution, metabolism and elimination studies and toxicokinetic studies

- Studies aimed at characterizing:
  - Changes in the metabolism of BPAF with life stage
  - Persistence of BPAF

Specific Aim 3: Conduct multigenerational reproductive toxicity and developmental toxicity studies

- Additional endpoints may be included based on:
  - The results of the tier one study
  - Reported endocrine activities of BPAF
  - Reported effects of BPA

Significance and Expected Outcomes

- Identify hazards associated with exposure to BPAF
- Provide data on the potential for BPAF to induce toxicity consistent with that of a synthetic estrogen